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PATENT
Attorney Docket No. PH 97089 (5500*48)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF EXPRESS MAIL
(37 C.F.R § 1.10)

I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE, EXPRESS MAIL POST OFFICE TO ADDRESSEE" UNDER 37 C.F.R § 1.10, BEARING EXPRESS MAIL LABEL NO EK219526394 ON THIS 21st DAY OF June, 2000 AND IS ADDRESSED TO. ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231.

Diane C Pickering
BY Diane C Pickering

INT'L APPL. NO.: PCT/FR98/02819

INT'L FILING DATE: December 22, 1998

PRIORITY DATE: December 24, 1997

APPLICANT: Richard DEROSE
Alain SAILLAND

Art Unit: Unassigned

SERIAL NO.: To be assigned

Examiner: Unassigned

FILED: June 21, 2000

FOR: METHOD FOR ENZYMATIC PREPARATION OF HOMOGENTISATE

Asst. Commissioner for Patents and Trademarks
Box PCT
Washington, D.C. 20231

TRANSMITTAL OF APPLICATION PAPERS TO U.S. DESIGNATED\ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. § 371 (37 CFR 1.494 OR 1.495)

This transmittal letter is based upon Form PTO-1390.

The above-identified applicant has filed an International Application under the PCT and

International Application No. PCT/FR98/02819

hereby submit(s) to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is the FIRST submission of items concerning a filing under 35 U.S.C. §371.

2. [] This is the SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. §371.

3. [] This is an express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay.

4. [X] A proper Demand for International Preliminary Examination (IPE) was made to the appropriate Authority (IPEA) by the 19th month from the earliest claimed priority date (see attached .

5. [X] A copy of the International Application as amended (35 U.S.C. §371(c)(2)) -
   (a) [] is transmitted herewith (required when not transmitted by International Bureau).
   (b) [X] has been transmitted by the International Bureau.
   (c) [] is not required, as the application was filed in the United States Receiving Office (RO/US).

6. [] A translation of the International Application into the English language WILL FOLLOW.

7. [X] Amendments to the (specification and) claims of the International Application under PCT Article 19 (35 U.S.C. §371 (c)(3))
   (a) [] are transmitted herewith (required if not transmitted by the International Bureau).
   (b) [] have been transmitted by the International Bureau.
   (c) [] have not been made; however, the time limit for making such amendments has NOT expired.
   (d) [X] have not been made and will not be made.
   (e) [] will be submitted with the appropriate surcharge.

8. [] A translation of the amendments to the claims (and/or the specification) under PCT Article 19 (35 U.S.C. §173(c)(3)) is enclosed or will be submitted with the appropriate surcharge.

International Application No. PCT/FR98/02819

9. [] An unexecuted Oath or Declaration/Power of Attorney of the inventor(s) (35 U.S.C. §371(c)(4)) is enclosed.

10. [] A translation of at least the Annexes to the IPE Report under PCT Article 36 (35 U.S.C. §371(c)(5)) is enclosed.

Items 11. to 16. below concern other document(s) or information included:

11. [] An Information Disclosure Statement under 37 CFR 1.97 and 1.98 is enclosed.

12. [] An Assignment is enclosed for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31. is included.

13. [] **A FIRST preliminary amendment is enclosed. IT IS REQUESTED THAT THE FILING FEES FOR THE CLAIMS BE CALCULATED AFTER THE CLAIM AMENDMENTS IN THE PRELIMINARY AMENDMENT HAVE BEEN ENTERED.**

14. [] A substitute specification (including claims, abstract, drawing) is enclosed.

15. [] A change of Power of Attorney and/or address letter is enclosed.

16. [X] Other items of information:

[x] This application is being filed pursuant to 37 CFR 1.494(c) or 1.495(c), and any **missing parts** will be filed within the time period set in accordance with 35 C.F.R. 1.495(C).

[] 22 months from the priority date under 37 CFR 1.494(c), or

[] 32 months from the priority date under 37 CFR 1.495(c).

[] The undersigned attorney is authorized by the International application and by the inventors to enter the **National Phase** pursuant to 37 CFR 1.494(c) or 1.495(c).

The following additional information relates to the International Application:

[ ] Receiving Office: EPO (originally filed in the German Patent Office)

International Application No. PCT/FR98/02819

[x] IPEA (if filing under 37 CFR 1.495): EPO
[x] Priority claim(s) (35 USC §§ 119, 365): French 97/16727
Filed: December

[x] A copy of the International Search Report is
[x] enclosed.
[] attached to the copy of the International Application.

[x] A copy of the Receiving Office Request Form is enclosed.

17. [] Small Entity Form

The fee calculation is set forth below.

FEE CALCULATION

NOTE: IT IS REQUESTED THAT THE FILING FEES FOR THE CLAIMS BE CALCULATED AFTER THE CLAIM AMENDMENTS IN THE PRELIMINARY AMENDMENT HAVE BEEN ENTERED.

[x] A check in payment of the filing fee, calculated as follows, is attached (37 CFR 1.492)

Basic Fee	$840.00
Total Number of claims in excess of (20) times $18	$0.00
Number of independent claims in excess of (3) times $96	$0.00
Fee for multiple dependent claims $260	$260.00
TOTAL FILING FEE	$1100.00

Kindly send us the official filing receipt.

The Commissioner is hereby authorized to charge any additional fees which may be required or to credit any overpayment to Deposit Account No. 03-2775. This is a "general authorization" under 37 CFR 1.25(b), except that no automatic debit of the issue upon allowance is authorized. This letter is being submitted in triplicate.

Respectfully submitted,

CONNOLLY BOVE LODGE & HUTZ LLP

Date: June 21, 2000

By: _____

Robert G. McMorrow, Jr.
Reg. No. 30,962
1220 Market Street
P.O. Box 2207
Wilmington, DE 19899
Tel. (302) 658-9141

96874

Method for enzymatic preparation of homogentisate

The present invention relates to a novel method for enzymatic preparation of homogentisate, or 2,5-dihydroxyphenylacetic acid (hereafter HMO).

HMO is a known precursor of molecules termed ochronotic pigments which are melanin analogues. These brown molecules are, moreover, often cited as "melanin-like pigments" which find a varied application in cosmetics or the pharmaceutical industry. The addition of melanin or melanin-like pigments to antisun milks would have an advantageous protective effect. To produce these ochronotic derivatives from HGA, the method is simple since the molecule self-oxidizes rapidly under alkaline conditions. Various methods for enzymatic preparation of HMO from 1-phenylacetic acid or from tyrosine are described in the prior art (WO 93/08295 or EP 343 330), as well as the subsequent preparation of melanin.

It is also known that HMO is a compound which is essential to plant life. In plant cells, HMO is the product of enzymatic transformation of 4-hydroxyphenylpyruvate (hereafter HPP) with 4-hydroxyphenylpyruvate dioxygenase (hereafter HPPD). Inhibitors of this enzyme are herbicidal compounds which block the production of HMO in plant cells (Pallett K.E. et *al.* 1997 Pestic. Sci. 50 83-84). When plants of *Arabidopsis thaliana* for example, are

germinated on synthetic medium in the presence of an HPPD inhibitor, the plants will germinate, remain white and then die very rapidly. However, if HMO is added to the synthetic medium supplemented with an HPPD inhibitor, the plants will germinate normally and remain green as long as the medium contains HMO. It is thus also important to have HMO available to prevent deficiencies in plants which are linked to a natural or induced, in particular by HPPD inhibitors, metabolic dysfunction of HMO biosynthesis.

The present invention thus relates to a method for enzymatic preparation of HMO from HPP, and more particularly to a method for enzymatic preparation of HMO from HPPD-inhibitor-insensitive HPP.

The method according to the invention consists in carrying out, in a suitable reaction medium, the following enzymatic reactions:

- enzymatic conversion of HPP into 4-hydroxyphenyl-acetate (hereafter HPA) with a first suitable enzyme, then
- enzymatic conversion of HPA into HMO with a second suitable enzyme.

The following first enzymatic reaction

4-hydroxyphenylpyruvate (HPP) --->
4-hydroxyphenylacetate (HPA)

is catalysed by a suitable HPP-oxidase. Such oxidases are found in many prokaryotic or eukaryotic species, in particular in bacteria which can grow on HPP as the

only carbon source, transforming it into HPA, more particularly in an *Arthrobacter* in which such an oxidase [lacuna] responsible for a step in tyrosine catabolism (Blakley, E.R. 1977 Canadian Journal of Microbiology 23 1128-1139).

The following second enzymatic reaction:

4-hydroxyphenylacetate (HPA) ---> homogentisate (HMO)

is catalysed by a suitable HPA-hydroxylase. Such hydroxylases are found in many prokaryotic or eukaryotic species, in particular in bacteria which can grow on HPA as the only carbon source, transforming it into HMO, more particularly in *Pseudomonas acidovorans*, often termed *Comamonas acidovorans* (Hareland, W.A. et al 1975 Journal of Bacteriology 121 272-285), in certain *Xanthobacter* (Van Den Tweel W.J.J. et *al*. 1986 Antonie val Leeuwenhoek 52 309-318), in *Pseudomonas alcaligenes* (Karigar C.S. and Pujar B.G. 1993 FEMS Microbiology Letters 110 59-64), in *Flavobacterium sp.* (Van Den Tweel W.J.J. et *al*. 1988 Arch Microbiol. 149 207-213), in *Bacillus subtillis* (Crawford R.L. 1978 FEMS Microbiology Letters 4 233-234), in *Nocardia sp.* DM1 (Raju S.G. and Vaidyanathan C.S. 1986 J. Indian Inst. Sci. 66 511-520) and in *Rhodococcus erythropolis* (Suemori A. et *al*. 1996 Journal of Fermentation And Bioengineering Vol. 81, No. 2 133-137).

The HPA-hydroxylase used in the method according to the invention is advantageously extracted from *Pseudomonas acidovorans*.

According to a preferential embodiment of the invention, both enzymatic reactions are carried out in the same reaction medium containing HPP, the two suitable enzymes being present together at the same time in the reaction medium.

The two suitable enzymes can be introduced into the suitable reaction medium in the form of protein extract, said protein extract being able to be crude or totally or partially purified, or alternatively they can be produced in situ by suitable biological organisms. They can thus be produced in situ by each biological organism which naturally produces the two enzymes, or alternatively by a single biological organism which has been modified so as to produce the two enzymes. This biological organism can be a bacterium, a yeast or a plant cell.

Since the two enzymes are insensitive to HPPD inhibitors, the method according to the invention can be performed in the presence of an HPPD inhibitor in the suitable reaction medium.

The suitable reaction medium consists of any aqueous medium in which the temperature, pH and ionic strength conditions are suitable for the enzymatic reactions. When the enzymes are produced in situ by one

or more biological organisms, the reaction medium is suitable for the growth of said organisms.

At the end of the reaction, HMO can be isolated from the reaction medium and purified, or left in the reaction medium. In this second case, the reaction medium containing HMO can be used as a nutrient medium for culturing plants, more particularly for culturing plants which exhibit a natural or induced, in particular by HPPD inhibitors, metabolic dysfunction of HMO biosynthesis.

The examples below make it possible to illustrate the invention, without however seeking to limit the scope thereof.

Example 1: Production of HPA from HPP using a protein extract from *Arthrobacter*

Arthrobacter culture:

Arthrobacter globiformis is cultured at 28°C and 220 rpm for 20 hours in a 250-ml Erlenmeyer flask containing 50 ml of medium A supplemented with 0.1% L-tyrosine and 0.01% of yeast extract [medium A composed, in grams per litre, of KH_2PO_4 (1.5) $K_2HPO_4.3H_2O$ (3.5) NH_4NO_3 (1) $FeSO_4.7H_2O$ (0.1) $ZnSO_4.7H_2O$ (0.01) $NaMoO_2.7H_2O$ (0.01) $CaCl_2.2H_2O$ (0.01) $MgSO_4.7H_2O$ (0.05)].

Extraction and assay of HPP-oxidase activity

A cell pellet is recovered from 2.1 litres of culture by centrifugation at 3000 xg for 15 min. The pellet is washed with distilled water and then

recentrifuged. All subsequent steps are carried out at 4°C.

The cell pellet, which is approximately 3.4 g, is resuspended in 7 ml of extraction buffer (0.05 M potassium phosphate pH 7.5, 0.1 mM TPP, 0.1 mM $MgCl_2$ and 5 mM mercaptoethanol) and sonicated twice at 23 kHz for 2.5 min. The resulting suspension is centrifuged at 44,000 ×g for 20 min. The harvested supernatant is again centrifuged at 100,000 ×g for 60 min. 0.7 ml of 2% protamine sulphate in the extraction buffer is added to the new 7-ml supernatant, followed by gentle stirring. The precipitate which forms is removed by a centrifugation at 20,000 ×g for 20 min. Ammonium sulphate is gradually added to the supernatant thus obtained so as to reach 60% saturation. This new preparation is stirred for 30 min., and the precipitate formed harvested by centrifugation at 20,000 ×g for 20 min. The pellet is redissolved in 0.5 ml of extraction buffer and aliquoted in 0.1-ml fractions, these fractions being kept at -80°C before use.

The HPP-oxidase activity is measured in a 96-well microtitration plate with 200 µl of reaction per well consisting of 149.8 µl of 67 mM sodium phosphate pH 7.4, 10 µl of 13.4 mM glutathione, 10 µl of 67 mM MgCl2, 10 µl of 26.7 mM TPP, 10 µl of 67 µM FAD, 0.2 µl of protein (i.e. approximately 6 µg) and 10 µl of 2.5 mM HPP.

When an assay for inhibition by an HPPD inhibitor is carried out, 2 µl of 10 mM 4-[4-trifluoromethyl-2-(methylsulphonyl)benzoyl]-5-cyclopropylisoxazole are added to a phosphate buffer containing 20% of DMSO.

The reaction is initiated by adding the substrate, HPP; it takes place at 30°C for 5 min. with stirring. The reaction is stopped by adding 33 µl of 25% perchloric acid.

The plate is then centrifuged at 2000 rpm for 15 min., and the supernatant is analysed by HPLC. 50 µl of the supernatant is injected onto a Spherisorb ODS2 column equilibrated with buffer A (5.5% acetonitrile, 0.1% TFA) at the flow rate of 1.5 ml/min.

The elution programme used is:

0 min.: 0% of buffer B (acetonitrile)

6 min.: 15% of buffer B

6.5 min.: 15% of buffer B

7 min.: 60% of buffer B

8 min.: 60% of buffer B

8.5 min.: 0% of buffer B

The detection is carried out at 276 nm.

The HPA produced by the enzymatic extract from HPP is compared with a reference consisting of commercial HPA, in terms of retention time and spectral absorption peak.

Results

The HPLC analysis shows that the protein extract extracted from *Arthrobacter globiformis* cultured on tyrosine as the major carbon source is capable of transforming the HPP into HPA (the molecule produced comigrates perfectly with the commercial reference HPA).

The enzyme responsible for this reaction is not inhibited by 100 µM of HPPD inhibitor.

Example 2: Production of HMO from HPA using a protein extract from *Pseudomonas*

Organism culture

Pseudomonas acidovorans is cultured at 28°C and 220 rpm for 20 hours in a 250-ml Erlenmeyer flask containing 50 ml of medium B supplemented with 0.15% HPA and 0.01% of nitrilotriacetic acid [medium B composed, in grams per litre, of NaH_2PO_4 (1) $K_2HPO_4.3H_2O$ (4.25) NH_4Cl (2) $FeSO_4.7H_2O$ (0.012) $ZnSO_4.7H_2O$ (0.003) $MnSO_4.7H_2O$ (0.003) $CoSO_4.7H_2O$ (0.01) $MgSO_4.7H_2O$ (0.2)].

Extraction and assay of HPA-hydroxylase activity

A cell pellet is recovered from 0.1 litre of culture by centrifugation at 7500 ×g for 10 min. The pellet is washed with distilled water and then recentrifuged. All subsequent steps are carried out at 4°C.

The cell pellet, which is approximately 0.5 g, is resuspended in 1.5 ml of extraction buffer

(0.1 M potassium phosphate pH 7.2, 1 mM DTE and 5 mM $MgMgSO_4$) and sonicated twice at 23 kHz for 2.5 min. The resulting suspension is centrifuged at 44,000 ×g for 20 min. The harvested supernatant is again centrifuged at 100,000 ×g for 60 min. The new supernatant is aliquoted in 0.1-ml fractions, these fractions being kept at -80°C before use.

The HPA-hydroxylase activity is measured in a 96-well microtitration plate with 200 µl of reaction per well consisting of 150 µl of 0.1 M sodium phosphate pH 7.2, 10 µl of 20 mM DTE, 10 µl of 3 mM NADH, 15 µl of 67 µM FAD, 10 µl of protein (i.e. approximately 7 µg) and 5 µl of 10 mM HPA.

When an assay for inhibition by an HPPD inhibitor is carried out, 2 µl of 10 mM 4-[4-trifluoromethyl-2-(methylsulphonyl)benzoyl]-5-cyclopropylisoxazole are added to a phosphate buffer containing 20% of DMSO.

The reaction is initiated by adding the substrate, HPA; it takes place at 30°C for 5 min. with stirring. The reaction is stopped by adding 33 µl of 25% perchloric acid.

The plate is then centrifuged at 2000 rpm for 15 min., and the supernatant is analysed by HPLC. 10 µl of the supernatant is injected onto a Spherisorb ODS2 column equilibrated with buffer A (5.5% acetonitrile, 0.1% TFA) at the flow rate of 1.5 ml/min.

The elution programme used is:

0 min.: 0% of buffer B (acetonitrile)

0.8 min.: 0% of buffer B

1 min.: 60% of buffer B

1.7 min.: 60% of buffer B

1.9 min.: 0% of buffer B

5 min.: 0% of buffer B

The detection is carried out at 292 nm.

The HMO produced by the enzymatic extract from HPA is compared with a reference consisting of commercial HMO, in terms of retention time and spectral absorption peak.

Results

The HPLC analysis made it possible to show that the protein extract extracted from *Pseudomonas acidovorans* is capable of transforming the HPA into HMO (the molecule produced comigrates perfectly with the commercial reference HMO).

The enzyme responsible for this reaction is not inhibited under our assay conditions by 100 µM of HPPD inhibitor.

Example 3: Production of HMO from HPP using a protein extract from *Arthrobacter* and from *Pseudomonas*

HPA-hydroxylase activity-coupled HPP-oxidase activity

The HPA-hydroxylase activity-coupled HPP-oxidase activity is measured in a 96-well microtitration plate with 200 µl of reaction per well

consisting of 100 µl of 100 mM sodium phosphate pH 7.2, 10 µl of 20 mM DTE, 10 µl of 3 mM NADH, 15 µl of 67 µM FAD, 10 µl of 13.4 mM glutatione, 10 µl of 67 mM MgCl2, 10 µl of 26.7 mM TPP, 2 µl of HPP-oxidase extract (i.e. approximately 60 µg), 25 µl of HPA-hydroxylase extract (i.e. approximately 18 µg) and 10 µl of 10 mM HPP.

The reaction is initiated by adding the substrate, HPP; it takes place at 30°C for 30 min. with stirring. The reaction is stopped by adding 33 µl of 25% perchloric acid.

The plate is then centrifuged at 2000 rpm for 15 min., and the supernatant is analysed by HPLC. 25 µl of the supernatant is injected onto a Spherisorb ODS2 column equilibrated with buffer A (5.5% acetonitrile, 0.1% TFA) at the flow rate of 1.5 ml/min.

The elution programme used is:

0 min.: 0% of buffer B (acetonitrile)

6 min.: 15% of buffer B

6.5 min.: 15% of buffer B

7 min.: 60% of buffer B

8 min.: 60% of buffer B

8.5 min.: 0% of buffer B

The detection is carried out at 276 nm and 292 nm simultaneously.

Results

The HPLC analysis made it possible to show that the protein extract extracted from *Arthrobacter globiformis* combined with that from *Pseudomonas*

acidovorans is capable of simultaneously transforming HPP into HMO (the molecule produced comigrates perfectly with the commercial reference HMO).

Claims

1. Method for enzymatic preparation of homogentisate (HMO) from 4-hydroxypyruvate (HPP), characterized in that it consists in carrying out, in a suitable reaction medium, the following enzymatic reactions:

- enzymatic conversion of HPP into 4-hydroxyphenyl-acetate (HPA) with a first suitable enzyme, then
- enzymatic conversion of HPA into HMO with a second suitable enzyme.

2. Method according to Claim 1, characterized in that the first enzymatic conversion is catalysed by a suitable HPP-oxidase.

3. Method according to Claim 2, characterized in that the HPP-oxidase originates from bacteria which can grow on HPP as the only carbon source.

4. Method according to Claim 2, characterized in that the HPP-oxidase originates from *Arthrobacter*.

5. Method according to Claim 1, characterized in that the second enzymatic conversion is catalysed by a suitable HPA-hydroxylase.

6. Method according to Claim 5, characterized in that the HPA-hydroxylase originates from bacteria which can grow on HPA as the only carbon source.

7. Method according to Claim 6, characterized in that the bacteria are chosen from *Pseudomonas acidovorans, Xanthobacter, Pseudomonas alcaligenes, Flavobacterium sp., Bacillus subtillis, Nocardia sp.* DM1 and *Rhodococcus erythropolis*.

8. Method according to Claim 5, characterized in that the HPA-hydroxylase is extracted from *Pseudomonas acidovorans*.

9. Method according to one of Claims 1 to 8, characterized in that both enzymatic reactions are carried out in the same reaction medium containing HPP, the two suitable enzymes being present together at the same time in the reaction medium.

10. Method according to one of Claims 1 to 9, characterized in that the two suitable enzymes are introduced into the suitable reaction medium in the form of protein extracts, or alternatively they can be produced in situ by suitable biological organisms.

11. Method according to one of Claims 1 to 10, characterized in that it is carried out in the presence of an HPPD inhibitor in the suitable reaction medium.

COMBINED DECLARATION AND POWER OF ATTORNEY	Attorney Docket No. 5500*48 (PH 97089)

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

the specification of which

(check one) ☐ is attached hereto.

☒ was filed on June 21, 2000 as Application Serial No. 09/582,482
and PCT International application no. PCT/FR98/02819 filed December 22, 1998

was amended on _____ (if applicable)

was amended through _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed
FR 97 16727 (Number)	France (Country)	24 December 1997 (Day/Month/Year Filed)	☒ Yes ☐ No
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	☐ Yes ☐ No
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	☐ Yes ☐ No

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

_____ (Application No.) _____ (filing date)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

PCT/FR98/02819 (Application Serial No.)	22 December 1998 (Filing Date)	_____ (Status)
_____ (Application Serial No.)	_____ (Filing Date)	_____ (Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

In the matter of the above-identified application, please recognize Rudolf E. Hutz, Reg. No. 22,397; John D. Fairchild, Reg. No. 19,756; Harold Pezzner, Reg. No. 22,112; Richard M. Beck, Reg. No. 22,580; Paul E. Crawford, Reg. No. 24,397; Patricia Smink Rogowski, Reg. No. 33,791; Robert G. McMorrow, Jr., Reg. No. 30,962; Ashley I. Pezzner, Reg. No. 35,646; William E. McShane, Reg. No. 32,707; Mary W. Bourke, Reg. No. 30,982; Gerard M. O'Rourke, Reg. No. 39,794; James M. Olsen, Reg. No. 40,408; Francis DiGiovanni, Reg. No. 37,310; Eric J. Evain, Reg. No. 42,517; Daniel C. Mulveny, Reg. No. 45,897; Christine M. Hansen, Reg. No. 40,634; Patrick H. Higgins 39,709 and Elliot C. Mendelson (Agent), Reg. No. 42,878, all of P.O. Box 2207, Wilmington, Delaware 19899-2207 as attorneys with full power of substitution to prosecute this application and conduct all business in the Patent and Trademark Office connected therewith.

Send Correspondence To: Connolly Bove Lodge & Hutz LLP, P.O. Box 2207, Wilmington, Delaware 19899-2207	Direct Telephone Calls To: (302) 658-9141

FULL NAME OF SOLE OR FIRST INVENTOR	INVENTOR'S SIGNATURE	DATE
Richard Derose	Richard DeRose	9/14/2000
RESIDENCE: 31, rue du Bois Guillaume, 91000 Evry, France FRX		CITIZENSHIP: USA
POST OFFICE ADDRESS: 31, rue du Bois Guillaume, 91000 Evry, France		
FULL NAME OF SECOND JOINT INVENTOR IF ANY	INVENTOR'S SIGNATURE	DATE
Alain Sailland	Alain Sailland	9/29/2000
RESIDENCE: 38, rue Albert Chalinel, 69009 Lyon, France FRX		CITIZENSHIP: France
POST OFFICE ADDRESS: 38, rue Albert Chalinel, 69009 Lyon, France		
FULL NAME OF THIRD JOINT INVENTOR IF ANY	INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP
POST OFFICE ADDRESS		
FULL NAME OF FOURTH JOINT INVENTOR IF ANY	INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP
POST OFFICE ADDRESS		
FULL NAME OF FIFTH JOINT INVENTOR IF ANY	INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP
POST OFFICE ADDRESS		
FULL NAME OF SIXTH JOINT INVENTOR IF ANY	INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP
POST OFFICE ADDRESS		

::ODMA\MHODMA\CB;100982;1